Eight-membered Ring Formation via Olefin Insertion into a Carbon–Carbon Single Bond

Takanori Matsuda, Atsushi Fujimoto, Mitsuru Ishibashi, and Masahiro Murakami*
Department of Synthetic Chemistry and Biological Chemistry, Graduate School of Engineering, Kyoto University,
Katsura, Kyoto 615-8510

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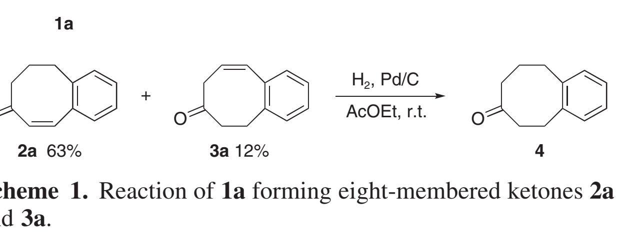
Treatment of cyclobutanone having an *o*-styryl group at the 2-position with a catalytic amount of rhodium–phosphine complex afforded eight-membered ring ketones via intramolecular insertion of the C=C bond into the C–C single bond of the cyclobutanone.

Cleavage of a carbon–carbon single bond by transition metals is potentially an attractive elementary step in the development of new catalytic organic transformations.[1] We have found that rhodium(I) complexes can undergo insertion into the bond between the carbonyl carbon and the α-carbon of cyclobutanones.[2] The potential of this elementary step was demonstrated by the successful intramolecular olefin insertion reaction into a carbon–carbon single bond that constructs a complex bicyclo[3.2.1] skeleton from 3-(*o*-styryl)cyclobutanone in a single step.[3] An increase of the repertoire of applications expands the synthetic potential of the transition-metal catalyzed carbon–carbon bond cleaving reactions. On the other hand, eight-membered carbocycles are often an important structural feature of biologically active compounds. Therefore, the development of new methods for their synthesis has been a continuing challenge, although a formidable objective.[4] The new olefin insertion reaction reported herein constructs eight-membered carbocyclic rings from 2-(*o*-styryl)cyclobutanone in a single chemical operation with good atom economy.

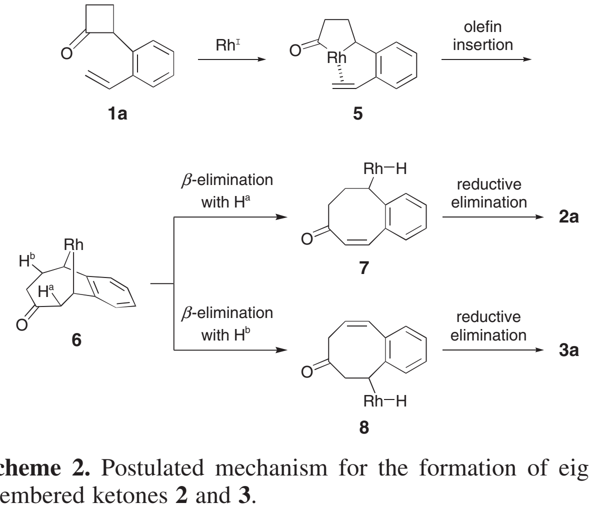
Cyclobutanone **1a**, equipped with an *o*-styryl group at the 2-position, was prepared from 2-vinylbenzaldehyde according to the Trost's method.[5] 2-(*o*-Styryl)cyclobutanone **1a** thus obtained was heated to 140 °C in *m*-xylene in the presence of a rhodium complex prepared in situ from $[\mathrm{Rh(cod)_2}]\mathrm{PF_6}$ (5 mol %, cod = cycloocta-1,5-diene)[6] and a phosphine ligand. When tris(*o*-methoxyphenyl)phosphine (24 mol %) was used as the ligand, substrate **1a** was consumed after 24 h. Chromatographic isolation afforded a mixture of unsaturated eight-membered ring ketones (**2a** and **3a**, 84:16) in 75% combined yield (Scheme 1).[7] A small amount (ca. 10% by GC) of decarbonylation products, i.e., *o*-cyclopropylstyrene and 1-[(*E*)-prop-1-en-1-yl]-2-vinylbenzene were formed as the by-products. Decreasing the phosphine loading (6 mol %) led to the formation of a significant amount (47% by GC) of the decarbonylation products. Hydrogenation of a mixture of **2a** and **3a** over palladium on charcoal gave the single product **4** in 95% yield, providing further support for the structures of **2a** and **3a**.



Scheme 1. Reaction of **1a** forming eight-membered ketones **2a** and **3a**.

The following mechanism, shown in Scheme 2, explains the formation of the isomeric unsaturated eight-membered ring ketones **2a** and **3a** from **1a**. Rhodium(I) initially undergoes insertion between the carbonyl carbon and the substituted α-carbon to afford the five-membered acylrhodium intermediate **5**. The vinyl group might coordinate to rhodium, thereby directing it to the proximal α-bond, although substantial acceleration was not observed in comparison to the former examples.[2,3] Then migratory insertion of the vinyl group into the rhodium–acyl carbon bond generates the bicyclic intermediate **6**.[8] Subsequent β-elimination of $\mathrm{H^a}$ located α to the carbonyl group furnishes the intermediate **7** having an eight-membered ring skeleton. Subsequent reductive elimination gives rise to the product **2a** with the regeneration of the rhodium(I) species. Compound **3a** also arises from **6**, via β-elimination of $\mathrm{H^b}$ located β to the carbonyl group as shown in Scheme 2.[9] Facility of the β-hydride elimination would be affected by the dihedral angle $\mathrm{Rh–C–C–H^{a\ or\ b}}$.

Phosphine ligands other than tris(*o*-methoxyphenyl)phosphine were also examined. The use of more electron-donating trialkylphophines, like $\mathrm{P(}n\mathrm{\text{-}Bu)_3}$, P(*cyclo*-Hex)$_3$, and P(*t*-Bu)$_3$, resulted in the formation of a complex mixture of products. Among triarylphosphines, triphenylphosphine and tris(*p*-methoxyphenyl)phosphine gave very poor yield of **2a** and **3a**. Interestingly, triarylphosphines having *o*-methoxyphenyl groups worked well to afford the eight-membered ring products, although the reason for this is unclear (Table 1). Bis(*o*-methoxyphenyl)phenylphosphine gave a result comparable to tris(*o*-



Scheme 2. Postulated mechanism for the formation of eight-membered ketones **2** and **3**.

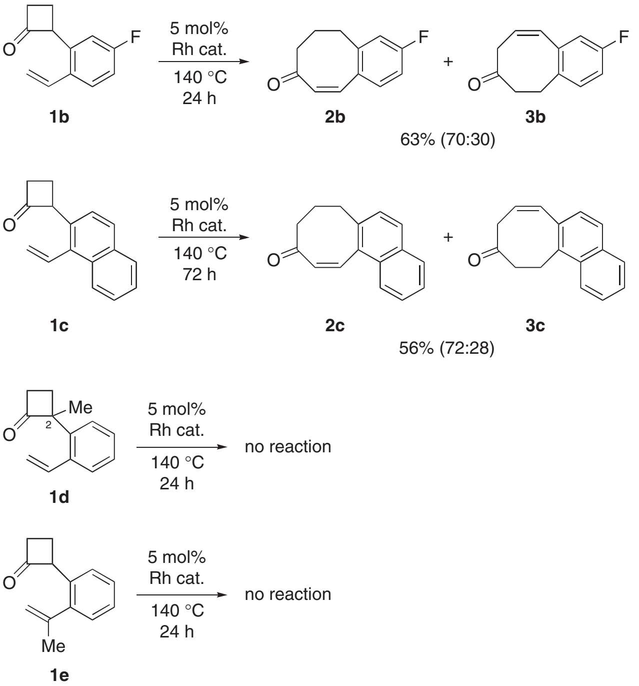
Table 1. Effect of phosphine ligands in the rhodium-catalyzed eight-membered ketone formation[a]

Entry	Phosphine	Ratio[b] **2a** :	**3a** :	Decarbonylation Products
1	$P(o\text{-}MeOC_6H_4)_3$	75	12	13
2[c]	$P(o\text{-}MeOC_6H_4)_3$	77	14	9
3	$PPh(o\text{-}MeOC_6H_4)_2$	63	18	19
4[d]	$PPh_2(o\text{-}MeOC_6H_4)$	41	14	45

[a]Conditions: Cyclobutanone **1a**, $[Rh(cod)_2]PF_6$ (5 mol %), and phosphine (36 mol %) were heated in *m*-xylene at 140 °C for 24 h unless otherwise noted. [b]Determined by ^1H NMR of the crude reaction mixture. [c]Result with 24 mol % of phosphine. [d]Starting material **1a** remained (29%).

methoxyphenyl)phosphine. (*o*-Methoxyphenyl)diphenylphosphine exhibited an inferior activity. Use of bidentate phosphines, $Ph_2P(CH_2)_nPPh_2$ ($n = 2$, 3, and 4), resulted in the predominant formation of the decarbonylation products (not shown in the table).

Other examples of the rhodium-catalyzed olefin insertion reaction are shown in Scheme 3. With 2-(*o*-styryl)cyclobutanone having a fluoro group *para* to the vinyl group **1b** and naphthalene derivative **1c**, the *o*-vinyl groups were successfully inserted between the carbonyl carbon and the proximal α-carbon to afford the corresponding eight-membered ring unsaturated ketones. The conjugated α,β-unsaturated ketones **2** predominated in both cases. However, 2-(*o*-styryl)cyclobutanone having an additional methyl group at the 2-position **1d** failed to undergo the rhodium-catalyzed reaction, probably due to the increased steric congestion between the acyl carbon and the quaternary α-carbon. An analogous olefin insertion also failed with substrate **1e** having a methyl group at the vinylic position, probably owing to steric reasons.



Scheme 3. Rhodium-catalyzed eight-membered ketone formation.

In summary, a new catalyzed insertion reaction of an olefin into a carbon–carbon single bond was developed. Although the full potential awaits further exploration, the present study demonstrates that the carbon–carbon bond cleavage provides a viable elementary step for target-directed synthesis.

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References and Notes

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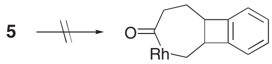
6 Only decarbonylation products were formed with the use of neutral rhodium $[RhCl(cod)]_2$ instead of the cationic complex.

7 **2a**: ^1H NMR ($CDCl_3$, 400 MHz) δ 2.08 (quint, $J = 6.7$ Hz, 2H), 2.35 (t, $J = 6.6$ Hz, 2H), 2.78 (t, $J = 6.8$ Hz, 2H), 6.16 (d, $J = 12.8$ Hz, 1H), 7.11 (d, $J = 12.8$ Hz, 1H), 7.24–7.37 (m, 4H); ^{13}C NMR δ 32.0, 32.5, 37.9, 126.5, 129.7, 129.9, 130.8, 132.0, 135.7, 140.8, 141.2, 204.3; HRMS (EI) calcd for $C_{12}H_{12}O$ 172.0888, found 172.0885. Anal. Calcd for $C_{12}H_{12}O$: C, 83.69; H, 7.02. Found: C, 83.49; H, 7.05%. **3a**: ^1H NMR ($CDCl_3$, 300 MHz) δ 2.58–2.64 (m, 2H), 2.95–3.00 (m, 2H), 3.02 (dt, $J = 7.4$, 0.6 Hz, 2H), 5.93 (dt, $J = 10.8$, 7.4 Hz, 1H), 6.70 (d, $J = 10.8$ Hz, 1H), 7.23–7.38 (m, 4H); ^{13}C NMR δ 30.7, 43.9, 44.7, 125.6, 126.7, 127.9, 128.4, 129.8, 132.3, 135.8, 139.0, 208.1.

8 Migratory insertion into the other rhodium–carbon(sp^3) linkage forming a highly strained benzocyclobutene skeleton is unlikely.



9 No unsaturated products resulting from further β-hydride elimination from **7** and **8** were observed.

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